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Clinical Characteristics and Treatment Resistance of Trigeminal Neuralgia in Multiple Sclerosis Patients: A Retrospective Observational Study

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ABSTRACT

Introduction: Trigeminal neuralgia (TN) is a neuropathic pain syndrome characterized by sudden, severe, and short-lived pain attacks in the facial region. When TN is associated with multiple sclerosis (MS), it may present distinct clinical features. The frequency of refractory TN and treatment responses in MS patients remain controversial in the literature. This study aims to investigate the clinical characteristics of MS-associated TN and assess whether TN is more treatment-resistant in MS patients.

Methods: This retrospective observational study analyzed the clinical and demographic data of patients diagnosed with TN and MS who presented to the Neurology Outpatient Clinic of Ankara Bilkent City Hospital between 2019 and 2025. The study included 36 MS patients with TN and 36 TN patients without MS, matched for age and sex. Variables such as age, sex, disease duration, MS type, Expanded Disability Status Scale (EDSS) score, TN onset age, TN treatment history, and magnetic resonance (MR) imaging findings were recorded. Refractory TN was defined as TN that did not respond to first- and second-line pharmacological treatments and required interventional procedures.

Results: The mean age of MS patients with TN was 51.19±10.78, similar to that of non-MS TN patients (p=0.97). While no significant differences were found in TN clinical characteristics between groups, MRI revealed a higher frequency of TN-associated brainstem lesions in MS patients (p=0.04). The rates of local anesthetic ganglion block and radiofrequency ablation were significantly higher in MS patients (p=0.01, p=0.02). Barrow Neurological Institute Pain Scale (BNI-PS) scores were significantly higher in MS patients (p=0.001), and the prevalence of refractory TN was markedly greater in the MS group (p=0.01). A positive correlation was observed between refractory TN and EDSS scores in MS patients (p=0.002, r=0.482).

Conclusion: This study demonstrates that TN is more resistant to treatment in MS patients, with a higher prevalence of refractory TN. Furthermore, the increased pain severity and greater need for interventional treatments in MS patients suggest that alternative management strategies are required for MS-associated TN. Larger-scale prospective studies are needed to evaluate treatment responses and long-term outcomes in this population.

Keywords: Multiple sclerosis; refractory trigeminal neuralgia; treatment-resistant neuralgiform pain

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INTRODUCTION

Trigeminal neuralgia (TN) is a neuropathic pain syndrome characterized by sudden, intense, and short-lasting facial pain attacks. The pain typically affects one or more branches of the trigeminal nerve and often severely limits daily functioning. The prevalence of TN is notably higher among individuals with multiple sclerosis (MS) compared to the general population, with an estimated rate ranging between 1.9% and 4.9% (1).

TN associated with MS may differ clinically from classical TN, and such differences can influence diagnostic and therapeutic strategies. In MS patients, TN tends to manifest at an earlier age (typically between 40 and 50 years) and is more frequently bilateral. While the pain is often described as sudden, shock-like, and brief, some patients may also experience continuous background pain (2,3).

There is ongoing debate in the literature regarding the frequency of refractory TN in MS patients and their response to treatment, with no clear consensus (4). Some studies report a higher prevalence of treatment-resistant TN in MS patients and a lower success rate with standard therapies (5). For example, one study found that TN in MS patients was less responsive to conventional treatments and that

Highlights

- **TN in MS patients is more frequently refractory, requiring more interventional treatments.**
- **BNI-PS scores were higher in MS patients with TN, indicating significantly increased pain severity.**
- **MRI revealed a higher prevalence of TN-associated brainstem lesions in MS patients.**

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these patients often had greater difficulty achieving pain control (6). Conversely, other studies have reported no significant difference in treatment outcomes between TN patients with and without MS (7). As a result, the efficacy of TN therapies in MS and the extent of benefit derived by these patients remain unclear, highlighting the need for further investigation (4).

The present study aims to provide a detailed analysis of the clinical features of MS-associated TN and to compare them with those of TN in patients without MS. Additionally, it investigates the degree of treatment resistance and the response to different therapeutic interventions in both groups to determine whether any statistically significant differences exist.

METHODS

Study Design and Patient Selection

This retrospective observational study was conducted to evaluate the clinical and demographic data of patients diagnosed with TN and MS who presented to the Neurology Outpatient Clinic of Ankara Bilkent City Hospital between 2019 and 2025. Patients were identified retrospectively through hospital automation systems using diagnostic codes (G35 – Multiple Sclerosis, G50.0 – Trigeminal Neuralgia), and their clinical data were retrieved from hospital records. The study received ethical approval from the institutional review board of Ankara Bilkent City Hospital and was conducted in accordance with the Declaration of Helsinki, with full protection of patient confidentiality.

Inclusion criteria:

- Diagnosis of MS according to the 2017 McDonald criteria (8)
- Diagnosis of TN according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) by the International Headache Society (9)
- At least one presentation to the Neurology Outpatient Clinic during the study period
- Complete and accessible medical records

Exclusion criteria:

- Incomplete or insufficient clinical data
- Facial pain syndromes associated with other neurological conditions
- Presence of another primary or secondary neuropathic pain syndrome
- Patients under 18 years of age or pregnant

Data Collection and Evaluation

A total of 4,221 MS patients, 1,398 TN patients, and 52 individuals diagnosed with both conditions were identified. Among those with both diagnoses, 36 patients (22 women and 14 men) with complete medical records were included. Additionally, 36 age- and sex-matched TN patients without MS were randomly selected via software for comparison.

The following variables were recorded for all participants: age, sex, age at disease onset, MS subtype (Relapsing-Remitting MS [RRMS], Secondary Progressive MS [SPMS], Primary Progressive MS [PPMS]), EDSS score, disease duration, MS medications, TN onset age, TN disease duration, previous treatments (pharmacotherapy, local anesthetic ganglion or cranial nerve branch blocks, radiofrequency ablation, or surgical interventions), side of TN (unilateral or bilateral), and MRI findings of pontine lesions consistent with TN.

The drugs used in the treatment of MS were categorized as follows: interferon Beta-1a, interferon Beta-1b, glatiramer acetate, teriflunomide, and dimethyl fumarate were classified as Group 1; fingolimod, cladribine, and natalizumab as Group 2; and ocrelizumab and alemtuzumab as Group 3.

For TN, the definition of refractory was applied to cases in which patients did not obtain sufficient benefit from treatment despite the use of first-line drugs such as carbamazepine and oxcarbazepine, or second-line drugs such as lamotrigine, baclofen, gabapentin, and pregabalin, either alone or in combination. It was also applied to cases in which patients underwent local anesthetic agent injections targeting branches of the trigeminal nerve, ganglion blockade, sphenopalatine or Gasserian ganglion block, trigeminal nerve branch block, radiofrequency (RF) ablation, or trigeminal neuralgia surgery (10).

The BNI-PS scores of the patients were retrospectively evaluated to determine the severity of TN pain and its impact throughout the disease course (11). According to this scale, the severity of TN is classified into five grades (I – no pain, no treatment required for TN; II – occasional pain, does not require treatment for TN; III – mild pain, adequately controlled with medications; IV – mild pain, not adequately controlled with medications; V – severe pain or no pain relief).

Statistical Analysis

Data were analyzed using SPSS version 26 and Python. Continuous variables were expressed as mean ± standard deviation (SD), median (IQR), and minimum–maximum values. Categorical variables were presented as counts and percentages. For the comparison of continuous variables between two groups, the Independent Samples t-test (for parametric data) or Mann-Whitney U test (for non-parametric data) was used. The Kruskal-Wallis test was applied for comparisons involving three or more groups with non-parametric distributions.

Associations between categorical variables were analyzed using the Chi-square test. Spearman's correlation analysis was employed to evaluate relationships between variables such as MS disease duration, EDSS scores, and BNI-PS scores. Post-hoc pairwise comparisons (Mann-Whitney U or Chi-square tests) were conducted with Bonferroni correction where significant differences were found. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean ages of TN patients with and without MS were 51.19 ± 10.78 and 51.11 ± 10.31 years, respectively, with no significant difference in age or sex distribution between the two groups ($p=0.97$, $p=1$). Similarly, no statistically significant differences were observed between the groups in terms of age at TN diagnosis or TN disease duration ($p=0.49$, $p=0.15$). Among the MS patients included, 16 were diagnosed with RRMS, 17 with SPMS, and 3 with PPMS, with a mean EDSS score of 4.25 ± 1.93.

There was no significant difference between groups regarding the laterality of TN (unilateral vs. bilateral; $p=1$). However, brainstem lesions consistent with TN were more frequently observed on MRI in MS patients compared to those without MS ($p=0.04$). The number of medications prescribed for TN did not differ significantly between groups ($p=0.24$), yet the frequency of local anesthetic ganglion or trigeminal nerve branch blocks and radiofrequency ablation was significantly higher in the MS group ($p=0.01$, $p=0.02$). Surgical intervention for TN was rare, with only one MS patient undergoing surgery.

The mean BNI-PS score was significantly higher in the MS group (3.33 ± 0.82) compared to the non-MS group (2.77 ± 0.59; $p=0.001$).

Among MS patients, a significant association was found between the number of medications used for TN and BNI-PS scores (p=0.01). Those who underwent ganglion or nerve block procedures had significantly higher BNI-PS scores (3.79 ± 0.69) than those who did not (3.05 ± 0.78; p=0.007). Similarly, MS patients who underwent radiofrequency ablation had higher BNI-PS scores (3.75 ± 0.75) than those who did not (3.13 ± 0.79; p=0.041).

The prevalence of refractory TN was significantly higher in the MS group compared to the non-MS group (p=0.01). Among MS patients, the presence of brainstem lesions on MRI was significantly associated with refractory TN (p=0.04). Refractory TN was also significantly more frequent among patients who had received pharmacological treatment for TN (p=0.004). MS patients who underwent ganglion or nerve block procedures or RF ablation were significantly more likely to have refractory TN (p<0.001 and p=0.001, respectively). The frequency of refractory TN was significantly higher among SPMS patients compared to those with RRMS (p<0.001). Furthermore, both EDSS and BNI-PS scores were significantly elevated in MS patients with refractory TN (p=0.005, p=0.04). A significant positive correlation was also found between EDSS and BNI-PS scores (p=0.002, r=0.482). Table 1 presents the clinical characteristics of patients with and without MS and the previously administered TN treatments.

DISCUSSION

Our findings revealed that brainstem lesions consistent with TN were more frequently observed in MS patients on MRI, reinforcing prior reports by Love and Coakham (12) and Truini et al. (13), which highlighted the impact of demyelinating MS lesions on the trigeminal nerve. The significant correlation between these lesions and the presence of refractory TN supports the hypothesis that MS plaques may directly contribute to the pathophysiology of TN in this population.

The higher frequency of trigeminal nerve lesions in MS may reflect a pathophysiological mechanism similar to that observed in optic neuritis (ON), the most common cranial nerve manifestation in MS, which occurs in approximately 50% of patients. This parallel may stem from shared histological characteristics. While myelin in the optic nerve is produced by oligodendrocytes, myelin in other cranial nerves, starting from the third, is primarily produced by Schwann cells. The entry zone of the trigeminal nerve, like the optic nerve, is also myelinated by oligodendrocytes, potentially rendering it more vulnerable to immune-mediated demyelination, similar to ON (14).

Another key finding was the significantly higher BNI-PS scores among MS patients, indicating more severe pain. These patients also had a higher frequency of refractory TN, as well as a greater need for interventional procedures such as ganglion/nerve blocks and RF ablation. The elevated BNI-PS scores in patients receiving these procedures further support the notion of more intense and treatment-resistant pain in MS-associated TN. These results are consistent with previous studies indicating reduced treatment response and more challenging pain control in this group (5,6).

The underlying pathophysiology of more severe and treatment-resistant TN in MS may involve several factors. Demyelination in the trigeminal root entry zone may disrupt normal conduction and facilitate ectopic discharges, lowering pain thresholds and intensifying paroxysmal attacks. Multiple lesions in different segments of the trigeminal nerve may result in a more diffuse and complex pain profile. Progressive axonal damage may further impair nerve function, complicating pain management. Moreover, neurovascular compression, which may be more common in MS, could heighten nerve irritability and resistance to treatment. Finally, central sensitization due to CNS changes in MS may amplify pain perception and contribute to treatment resistance (1).

In contrast, some prior studies have reported no significant difference in treatment outcomes between MS and non-MS TN patients (7). These discrepancies could be due to differences in study design, patient selection, or treatment protocols, highlighting the heterogeneous nature of MS-associated TN and the need for individualized treatment approaches.

Our finding that SPMS patients had a significantly higher frequency of refractory TN, along with higher EDSS scores among refractory cases, suggests that disease progression may exacerbate TN symptoms. This supports the hypothesis proposed by Laakso et al. (14) that axonal injury in MS may contribute to worsening TN. Understanding this relationship could inform the development of more targeted treatment strategies.

This study has several limitations. First, its retrospective design may have introduced bias due to incomplete or inconsistent data. The relatively small sample size may have limited statistical power and the ability to perform subgroup analyses. As a single-center study, its generalizability is also restricted. The retrospective assessment of BNI-PS scores may not fully capture patients' subjective pain experiences. Additionally, the potential influence of MS therapies on TN severity was not examined in detail, which may have impacted the interpretation of treatment outcomes.

Table 1. Clinical Characteristics of TN Patients With and Without MS and Previously Administered Treatments for TN

Variable	TN Patients With MS	TN Patients Without MS	p-value
TN Disease Duration (Mean ± SD, years)	5.42 ± 5.52	3.78 ± 3.97	0.15
Use of Medication for TN (Yes/No) (n, %)	33 (91.7%)	29 (80.6%)	0.31
Use of Two or More Medications for TN (n, %)	12 (33.3%)	9 (25.0%)	0.60
Brainstem or Trigeminal Nerve Lesion Consistent with TN (n, %)	17 (54.8%)	8 (26.7%)	0.04
BNI-PS Score (Mean ± SD)	3.75 ± 1.13	2.00 ± 0.93	0.001
Refractory TN (n, %)	15 (41.7%)	5 (13.9%)	0.01
Ganglion or Trigeminal Nerve Block with Local Anesthetic Agent (n, %)	14 (38.9%)	4 (11.4%)	0.01
Radiofrequency Ablation (n, %)	12 (33.3%)	3 (8.6%)	0.02

BNI-PS: Barrow Neurological Institute Pain Scale; MS: Multiple Sclerosis; RF: Radiofrequency; TN: Trigeminal Neuralgia

In conclusion, this study provides a comprehensive evaluation of the clinical features and treatment response of TN in patients with MS. Our findings suggest that TN in MS is more likely to be refractory and may require tailored management strategies. Personalized treatment approaches and multidisciplinary care may be particularly important for this patient population. Given the heterogeneity of MS-associated TN, further prospective, large-scale studies are needed—particularly those focusing on clinical variations in MS subtype, lesion localization, and the effectiveness of emerging therapies. Improving our understanding of these relationships will be essential in enhancing the quality of life for patients affected by both MS and TN.

Ethics Committee Approval: The research protocol was approved by the Ethics Committee of the Institute of Health Sciences, Ankara Yıldırım Beyazıt University (date: February 20, 2025; approval number: 02/1123).

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Conflict of Interest: The authors declared that there is no conflict of interest.

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REFERENCES

1. Di Stefano G, Maarbjerg S, Truini A. Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. J Headache Pain 2019;20:20. [Crossref]
2. Cruccu G, Biasiotta A, Di Rezze S, Fiorelli M, Galeotti F, Innocenti P et al. Trigeminal neuralgia and pain related to multiple sclerosis. Pain 2009;143:186-191
3. Truini A, Prosperini L, Calistri V, Fiorelli M, Pozzilli C, Millefiorini E et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. Neurology 2016;31:2094–2099. [Crossref]
4. Krishnan S, Bigder M, Kaufmann AM. Long-term follow-up of multimodality treatment for multiple sclerosis-related trigeminal neuralgia. Acta Neurochir (Wien) 2018;160:135-144. [Crossref]
5. Cheng JS, Sanchez-Mejia RO, Limbo M, Ward MM, Barbaro NM. Management of medically refractory trigeminal neuralgia in patients with multiple sclerosis. Neurosurg Focus 2005;15;18(5):e13. [Crossref]
6. Lee AT, Raygor KP, Elefant F, Ward MM, Wang DD, Barbaro NM, et al. Comparison of Stereotactic Radiosurgery and Radiofrequency Ablation for Trigeminal Neuralgia in Multiple Sclerosis Patients. Stereotact Funct Neurosurg 2020;98:378-385. [Crossref]
7. Noorani I, Lodge A, Vajramani G, Sparrow O. The Effectiveness of Percutaneous Balloon Compression, Thermocoagulation, and Glycerol Rhizolysis for Trigeminal Neuralgia in Multiple Sclerosis. Neurosurgery 2019;1;85(4):E684-E692. [Crossref]
8. Carroll WM. 2017 McDonald MS diagnostic criteria: Evidence-based revisions. Mult Scler 2018;24:92-95. [Crossref]
9. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38:1-211. [Crossref]
10. Chhaparwal Y, Kumar M, Chhaparwal S. Drug Therapy for Refractory Trigeminal Neuralgia- A Review. Biomed Pharmacol J 2021;14(2). [Crossref]
11. Chen HI, Lee JY. The measurement of pain in patients with trigeminal neuralgia. Clin Neurosurg 2010;57:129-133.
12. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. Brain 2001;124(Pt 12):2347-2360. [Crossref]
13. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. J Neurol 2013;260:351-367. [Crossref]
14. Laakso SM, Hekali O, Kurdo G, Martola J, Sairanen T, Atula S. Trigeminal neuralgia in multiple sclerosis: Prevalence and association with demyelination. Acta Neurol Scand 2020;142:139-144. [Crossref]